Review Article

Modifiable risk factors for patients undergoing lung cancer surgery and their optimization: a review

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Abstract: Enhanced recovery after surgery (ERAS) programs include a variety of pre-, intra- and post-operative interventions that seek to decrease the stress response to surgery and facilitate the recovery of surgical patients. There are a number of patient factors that may increase the risk of postoperative complications (POC) after lung cancer surgery and delay recovery. Some of these factors may be amenable to optimization preoperatively and potentially decrease the incidence of these complications. We have chosen to discuss the incidence and complications associated with factors we felt were both relatively common and significant contributors to POCs. For each of these factors we discuss potential avenues for optimization and the evidence for the resulting decrease in complications.

Keywords: Lung; surgery; anesthesia; complications

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Enhanced recovery after surgery (ERAS) is a multimodal perioperative care pathway designed to achieve early recovery for patients undergoing major surgery (1). A key characteristic of ERAS is that it includes pre-, intra- and post-operative interventions. An extensive evidence base now supports the role of ERAS in decreasing complications and length of stay, and ERAS pathways have been developed and evaluated in most surgical specialties. While general principles, such as avoidance of excess fluid administration and early nutrition and mobilization are common across ERAS pathways for different surgeries, some components are unique to specific surgeries and institutions. Due to the unique characteristics and complication profile of patients having lung surgery, as well as pulmonary physiology, ERAS for lung surgery requires inclusion of unique processes.

Depending on the definitions used and the extent of surgical insult, the risk of postoperative complications (POC) following lung cancer surgery ranges from 6.7% to 50% (2), while mortality from lobectomy ranges from 2–4%, sleeve lobectomy 2–11% and pneumonectomy 6–8% (3-7). A review by Rotman *et al.* details the risk of various pulmonary complications after lung cancer surgery. They found that ARDS has an incidence of approximately 5% after lung resection, persistent air leak ranges from 2–13%, pneumonia 2–22% and anastomotic dehiscence 6% (8). Atrial fibrillation has an incidence of 10–20% after lobectomy and up to 40% after pneumonectomy (9) and overall cardiac complications 18% (10). Clearly, with serious complication rates of 5% to greater than 40%, efforts to decrease adverse postoperative events are required.

To date, numerous ERAS pathways have been described for thoracic surgery. However, a generally agreed upon pathway, or an ERAS society thoracic-specific guideline, have yet to be published (1). A systematic review and metanalysis of randomized controlled trials of enhanced recovery protocols by Li in 2017 showed that there is

Table 1 Preoperative risk factors for post-operative complications

Score/study	Risk factor
Respiratory failure—Arozullah (15)	Type of surgery, emergency surgery, albumin level less than 30 g/L, BUN >10.71 mmol/L (30 mg/dL), partially of fully dependent functional status, chronic obstructive pulmonary disease (COPD) and age >60
Pneumonia—Arozullah (16)	Type of surgery, age, functional status, weight loss, COPD, general anesthesia, impaired sensorium, cerebral vascular accident, BUN level, transfusion, emergency surgery, long-term steroid use, smoking, and alcohol use
Pneumonia—Gupta (17)	Age, American Society of Anesthesiologists (ASA) class, COPD, dependent functional status, preoperative sepsis, smoking before operation, and type of operation
NSQIP	Age, sex, functional status, emergency case, ASA class, steroid for chronic condition, ascites, sepsis, ventilator dependence, disseminated cancer, hypertension, congestive heart failure, dyspnea, current smoker, history of COPD, dialysis and acute renal failure and diabetes, BMI
Thoracoscore (18)	Age, sex, ASA, performance, dyspnea, priority, procedure, diagnosis, comorbidities (smoking addiction, history of cancer, COPD, arterial hypertension, heart disease, diabetes mellitus, peripheral vascular disease, obesity and alcoholism)
ESOS.01 (19)	Age, ppoFEV1

BUN, blood urea nitrogen; BMI, body mass index.

substantial variation in the preoperative elements included in thoracic ERAS pathways (11). Those included in the review included one or more of the following: patient education/counseling, shortened fasting, prophylactic antibiotics, respiratory drug intervention, intensive pulmonary physiologic therapy, physical muscle exercise training, cardiopulmonary exercise testing and optimized diets. Other pathways have also included smoking cessation (12), and optimization of comorbidities (13).

Studies examining the impact of these ERAS pathways in thoracic surgery have yielded inconsistent results, potentially due to variation in pathway design. A systematic review by Fiore in 2016 found no significant difference in rates of complications, mortality or readmissions associated with ERAS (14). However, the overall quality of included studies was poor. Two subsequent retrospective reviews (10,13) did find a decrease in complications and LOS after lung surgery, while a third showed a significantly lower rate of morbidity (11).

To address the variability in thoracic ERAS pathway designs and the resultant outcomes, consideration should be given to the entirety of the perioperative period. However, the first step in successful application of ERAS must be preoperative patient optimization. In particular, preoperative ERAS interventions should include processes that target known risk factors for complications that can be modified in the period between the decision being made to operate and the surgical date; ideally components should have evidence supporting their efficacy or effectiveness. Fortunately, as detailed in *Table 1*, many studies are available which identify preoperative risk factors for POCs across all surgeries and some specifically in lung cancer surgery.

Many risk factors that have been identified in lung cancer surgery patients are not modifiable (such as age, sex and cancer severity). However, some potentially modifiable risk factors do exist; appropriate optimization before surgery of such factors could potentially decrease the incidence of POCs and help us achieve our goal of early recovery. Therefore, the objective of this review is to synthesize and describe preoperative components of ERAS pathways that address common and potentially modifiable risk factors for POCs after lung cancer surgery including: anemia, chronic obstructive pulmonary disease (COPD), smoking cessation, malnutrition, alcohol consumption and frailty. While our focus will be on lung cancer, it should be recognized that many of the interventions are applicable to patients having lung surgery for benign reasons, or esophageal surgery, particularly in the presence of similar risk factors. Where evidence is lacking, knowledge gaps and/or emerging strategies will be highlighted. To complete this review a broad online search of the relevant literature was performed using PubMed.

Frailty

Frailty is a multidimensional syndrome related to age- and disease-related deficits that accumulate across the lifespan (20,21). Due to the accumulation of deficits, people with frailty are vulnerable to stressors, and are at increased risk of adverse health outcomes. While data detailing the prevalence of frailty in lung surgery patients is limited, and dependent upon criteria and cut-offs employed, over 30% of older people having major inpatient surgery live with frailty (22).

Many frailty instruments have been described and studied in the perioperative period (23-25), and almost all are associated with a 2-fold or greater increase in risk for mortality, POCs, and loss of independence after surgery. The association of frailty with outcomes in thoracic surgery has been reviewed, and overall limited thoracic surgery-specific data is available (26). These data suggest that frailty may be more strongly associated with adverse outcomes in thoracic surgery than in other specialties (4- to 7-fold increase in odds of adverse events compared to 2- to 3-fold). However, the majority of available data rely upon the National Surgical Quality Improvement Program modified Frailty Index, which has significant issues with missing data and does not align with accepted methods for frailty index development (27).

Due to its multidimensional nature, frailty contributes to adverse outcomes through a variety of mechanisms. Most commonly, cognitive, physiologic, and physical vulnerability contribute to increased rates of delirium (28), complications (29) and higher rates of early mortality (30), and decreased function and need for institutional discharge respectively (24,31). Strategies to prevent postoperative delirium, such as enhanced orientation, maintenance of physiologic homeostasis, and early mobilization should be planned for prior to surgery (32). A growing evidence base suggests that centrally acting medication are unlikely to prevent delirium, and should be reserved for hyperactively delirious individuals who are at risk of causing harm to self or others (33). Exercise and nutritional prehabilitation can both decrease the severity of frailty itself (34,35), and in a low risk of bias randomized trial in major abdominal surgery, personalized exercise and nutritional prehabilitation was efficacious in decreasing complication rates by 31% (36). Preoperative collaboration with specialists in geriatric medicine is also recommended, and may contribute to improve survival, decreased length of stay, and reduced complication rates (37,38).

Consistent with best practice guidelines for preoperative evaluation of the older surgical patient (39) we recommend routine frailty assessment of older adults prior to thoracic surgery to guide risk communication and to allow for individualized optimization.

Anemia

Anemia is common in lung cancer surgery patients, with a reported prevalence of 26% (40). In addition to its high prevalence, anemia is also a risk factor for poor post-surgical outcomes, and is associated with a 2–3-fold increase in respiratory and infectious complications (41,42). A small study by Anile *et al.* found that in patients undergoing lung cancer surgery there was no correlation between anemia and rates of POCs but they did find that those who were anemic had higher rates of blood transfusion which were in turn associated with higher rates of POCs and SSIs (43). Studies also suggest that anemia is associated with decreased mid- and long-term survival (40,44). Debate continues as to whether anemia is a causative factor or a marker for severity of illness, and further research is required to determine whether correcting anemia results in improved outcomes. However, based on postulated pathways, and evidence from other surgical specialties (45,46), it is reasonable to assume that correction of anemia could result in better outcomes in lung surgery patients.

Although anemia can be corrected by transfusion of red blood cells, there is significant evidence to suggest that lung surgery patient (47) and non-lung surgery patients (48-50) who receive a transfusion are at an increased risk of POCs. Typically, transfusions are not recommended above a hemoglobin of 70 g/L, as increased complications can result from immune modulation, volume overload, transfusion reactions and the debated role of RBC transfusions on cancer recurrence (51-53). For these reasons many have advocated for treating the anemia preoperatively without transfusions. Existing literature suggests that optimizing hemoglobin decreases the need for transfusions in total joint arthroplasty and abdominal surgery (46,54,55), while also decreasing LOS (56). Therefore, the majority of evidence suggests it is reasonable to optimize patients' hemoglobin without transfusing red blood cells (as would their primary care physician) in the limited time available from diagnosis to surgery.

Treatment of anemia starts with identification of the underlying cause. Basic investigations should include complete blood count (CBC), ferritin, transferrin saturation, inflammatory markers (such as C-reactive protein) and renal function. The most common cause of anemia is iron deficiency, however the cancer-related inflammatory state and resultant iron sequestration may also contribute (57).

Multiple modalities exist for correction of preoperative anemia. Fortunately, as most anemia is iron-deficiency related, many preoperative anemias will be responsive to iron therapy. Oral iron supplementation can be effective (57), but certain factors limit its preoperative use. These include time to effect and variable absorption and tolerability, which can be made worse by the inflammatory state (58). With an expected time from diagnosis to surgery of less than 4 weeks according to jurisdictional and specialty society guidelines (59) a more viable option is the use of intravenous (IV) iron. With the use of IV iron a maximal response may be seen in 2–3 weeks depending on the dose and type of IV iron (60). If the cause of anemia is iron sequestration one could consider the use of recombinant erythropoietin (rEPO) (57). This is controversial in the setting of lung cancer as rEPO has been linked with an increase in mortality, thrombotic events and worse response to treatment in patients with an active malignancy. A thorough exploration of this issue is available (61). Due to these risks of rEPO in the context of an active malignancy, the American Society of Hematology only recommends rEPO if the anemia has arisen as a result of concomitantly administered chemotherapy and only to limit the need for transfusion (62). They do not comment on the surgical period. Because of the challenges in establishing the risk benefit ratio to the individual patient, as well as issues of timely access, the assistance of a hematologist or transfusion medicine specialist should be sought if planning the use of IV iron, and in particular rEPO before surgery.

We recommend screening for anemia and optimizing hemoglobin when possible.

Chronic obstructive pulmonary disease (COPD)

Over 40% of patients with lung cancer have COPD (63), a diagnosis which is associated with an approximately 3-fold increase in the rate of complications such as pneumonia and prolonged air leak, and a doubling of the risk of death following lung resection (64,65). Even patients with early or mild COPD face increased risk of adverse outcome (66), however, it is currently unclear the extent to which increasing COPD severity predicts increased risk (66,67).

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) guidelines suggest optimization of COPD management prior to surgery but offer no specific treatment recommendations for the perioperative period (68). The recommendation to optimize appears reasonable given the potential for COPD exacerbations in the postoperative period (69), and some evidence can be extrapolated to support specific strategies for optimization. Such strategies include medical therapy, pulmonary rehabilitation and smoking cessation (which we will cover separately).

The GOLD guidelines published in 2017 describe the approach to medical and non-medical management of COPD. With the diagnosis of COPD patients should begin therapy with an inhaled short acting Beta agonist to be used as needed. With a forced expiratory volume in 1 second (FEV1) <80% predicted patients should start using a long acting muscarinic antagonist (LAMA) or long acting beta agonist (LABA) or both based on symptoms (68). The 2017 GOLD guidelines have changed the role of inhaled glucocorticosteroids (ICS) and now reserve these for "patients with a history of exacerbations" despite appropriate treatment with long acting bronchodilators. In terms of perioperative-specific recommendations, the GOLD guideline states that "To prevent postoperative pulmonary complications, stable COPD patients clinically symptomatic and/or with limited exercise capacity should be treated with medically intensively before surgery, with all the measures already well established for stable COPD patients who are not about to have surgery." Other specialty society guidelines, such as the Canadian Thoracic Society, provide no specific recommendations (70), other than to escalate therapy in a stepwise fashion based on symptom control.

Given the limited time to optimize COPD in the preoperative period, it can be difficult to titrate therapy and observe response. There is, however, limited literature to help guide us in the preoperative period. Specifically, patients treated with chronic LAMAs or who start treatment with a LAMA for a new preoperative diagnosis of COPD have improved spirometry results (FVC, FEV1 and therefore predicted postoperative FEV1), symptoms and complications rates (71-73). The duration of therapy required to achieve these results ranged from 1 to 2 weeks. Despite the reduced reliance on ICS in the GOLD and other guidelines, there is some weak evidence suggesting a significant preoperative benefit in terms of decreased PPCs and improved FEV1 with the use of ICS (74). Systemic steroid therapy has also been described, however the evidence supporting this approach is limited and of poor quality (75). Our local approach has been to maximize the use of LAMAs followed by LAMA/LABA combinations and reserve ICSs for patients with very severe airflow restriction or more symptomatic patients with severe airflow restriction. Systemic steroids are usually reserved for patients who may be presenting with an exacerbation or very poorly controlled disease and usually in conjunction with a respirologist. This local approach is detailed in *Figure 1*.

Spirometry (FEV1/FVC <0.7)	Less symptomatic (see below for details)	More symptomatic (see below for details)	Rapid respirology referral (faxed consult)
FEV1 ≥80% (mild)	SABA prn	SABA prn	No
FEV1 =50–79% (moderate)	LAMA + SABA prn	LAMA/LABA + SABA prn	No
FEV1 =30–49% (severe)	LAMA/LABA + SABA prn	LAMA/LAMA + ICS + SABA prn	Yes* (for a new diagnosis only)
FEV1 <30% (very severe)	LAMA/LAMA + ICS + SABA prn	LAMA/LAMA + ICS + SABA prn	Yes* (all patients)

Figure 1 The Ottawa Hospital preoperative COPD optimization protocol (76). *, if the patient's surgery is in <2 weeks please use the inpatient consult service instead. Less symptomatic: no history of exacerbations in the past year (antibiotics, prednisone use, hospitalizations) and MRC dyspnea scale of 1–2; More symptomatic: history of exacerbations in the past year (antibiotics, prednisone use, hospitalizations) and/or MRC of 3–5; MRC dyspnea 3: walks slower than people of the same age on the level because of breathlessness or has to stop for breath when walking at own pace on the level. FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; SABA, short acting beta agonist; LAMA, long acting muscarinic antagonist; ICS, inhaled corticosteroid; MRC, Medical Research Council dyspnea.

Pulmonary rehabilitation is also recommended. GOLD guidelines recommend incorporating non-pharmacologic interventions such as pulmonary rehabilitation in a COPD management plan (68). Such interventions typically last 6–8 weeks and incorporate patient tailored aerobic, strength and respiratory muscle training. Rehabilitation is likely the most effective therapeutic strategy to improve shortness of breath, health status and exercise tolerance in COPD (77). The preoperative use of this intervention in high risk patients undergoing both abdominal and thoracic surgery significantly decreases postoperative pulmonary complications (PPCs) (36,78). The limitations of this therapy include variable rates of completion by patients, limited access to the required resources and a typically long program duration. Fortunately, there is evidence that shorter courses of prehabilitation are still associated with decreased PPCs. Meta analyses show that inspiratory muscle training was associated with a 50% decrease in PPCs (79,80). Factors associated with greater success included: supervised programs of at least 2-week duration, with each session lasting more than 15 minutes. Effectiveness was also increased with imposed load increment, and adding other modes of exercise. The possibility of using home-based programs increases the feasibility of this intervention for patients with limited local access to hospital resources. An interesting point to consider is that the improvement in aerobic capacity and spirometry results may change the operability of certain high risk patients based on improved predicted postoperative FEV1 allowing for expanded treatment options (81).

We recommend assessing the presence and severity of COPD followed by rapidly optimizing pharmaceutical therapy and initiating inspiratory muscle training for those at highest risk.

Smoking cessation

Although smoking cessation is a pillar of COPD management, we have described it separately due to the non-COPD associated impact of perioperative smoking. According to one population-based study, the prevalence of a smoking history in those undergoing surgery for lung cancer is upwards of 85% (82). This same study suggests that complications rates for current and past smokers is more than doubled that for non-smokers and the hospital mortality rates were almost four times as great. These assertions are supported by other studies (18,83,84), but the literature is not unanimous in these findings (85-87).

Despite the extremely addictive nature of nicotine, a comprehensive intervention defined as an in person intervention with follow up contact combined with nicotine replacement therapy can result in significant quit rates (88). A systematic review and metanalysis by Wong *et al.* showed that quitting can decrease the risk of wound infections, as well as PPCs (89). The cigarette free period required to impact outcomes would seem to be in the range of 4 weeks for PPCs and 3–4 weeks for wound complications; longer periods are typically associated with better outcomes (89). Interestingly some studies would suggest a benefit simply with abstinence on the day of surgery (90). Studies involving lung cancer surgery, despite showing a decreased complication rate in ex-smokers compared to current smokers, have failed to show the dramatic improvements realized in other types of surgery, unless the smoke free period was much longer (82,91). How long that period needs to be remains unclear. In fact a systematic review by Schmidt-Hansen *et al.* concluded that based on the limited information available they were unable to make firm conclusions regarding smoking cessation prior to lung cancer surgery (92). That is not to say that we should not strive for abstinence in our patients since the benefits of quitting in the long term may be very significant as evidenced by recent data showing a benefit on long term survival in those who quit (93). Furthermore, the non-cancer related benefits of smoking cessation cannot be overlooked.

We recommend initiating smoking cessation interventions due to the long-term health benefits of cessation despite the surprising lack of evidence for an acute perioperative impact.

Malnutrition

The prevalence of malnutrition in thoracic surgery patients varies depending on the definition studied. Less than 5% of patients are severely underweight, but biomarkers indicating malnutrition are present in up to 40% of pneumonectomy patients (94-97). Patients with malnutrition have a four-fold higher rate of mortality (98) and complications (94); in particular higher rates of fistula formation (99), discharge to extended care facility (100) and cancer recurrence (101).

Many ERAS society guidelines incorporate some form of nutrition therapy (ERAS) but the evidence for its use in lung cancer surgery is limited. Typically, nutritional therapies can be separated into nutritional support for patients with malnutrition and immunonutrition therapy. Malnourished patients classified as at severe risk using a Nutritional Risk Screening Score (NRS-2002) of 5 or more were found to have a 50% decrease in post-operative infectious and non-infectious complications when provided with nutritional support for 7 days before abdominal surgery (102). The 2018 American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on Nutrition Screening and Therapy Within a Surgical Enhanced Recovery Pathway supports screening for malnutrition and treatment of surgical patients (103). However, no specific recommendations for lung cancer patients exist, and our search yielded no trials of therapy aimed at lung cancer surgery patients. Outside of the surgical field, patients with COPD may benefit from nutritional support as peripheral and respiratory muscle function are improved (104). In summary, there appears to be benefit to nutritional support in malnourished patients that may generalize to lung cancer surgery patients. Clinicians should maintain awareness of severely malnourished patients as refeeding syndrome can occur (105).

Immunonutrition, based on the concept that surgical stress leads to a depletion of conditionally essential nutrients and a subsequently dysregulated immune response, involves supplementation with a variety of nutrients, commonly omega-3, arginine, nucleotides, antioxidants and vitamins or minerals (103). The 2018 American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on Nutrition Screening and Therapy within a Surgical Enhanced Recovery Pathway clearly discusses the limitations of the current literature surrounding immunonutrition. The majority of focus has been in the setting of high-risk gastrointestinal surgery. Current recommendations are to consider immunonutrition, but it is clear that further high-quality research is required in this field. There are 2 small positive studies supporting immunonutrition in lung cancer surgery (106,107). A recent metanalysis suggests decreased complications when immunotherapy is used; however, the apparent benefit was lost when analysis was limited to higher quality studies (108).

We recommend nutritional supplementation to all preoperative lung cancer patients with severe malnutrition (NRS-2002 of 5 or greater or equivalent scale). However, we find the evidence for immunonutrition too weak to support this intervention at this time.

Alcohol

Alcohol use disorder (AUD) is present in 2.5–12% of lung cancer surgery patients, (109-111) which is similar to the prevalence of AUD in the general population of the United States (8.25%). In addition to the multiple comorbidities associated with prolonged excessive alcohol consumption, a metanalysis showed that men who consume more than 36 g/day (approx. 3 drinks) and women 24 g/day (approx. 2 drinks) have a 50% greater risk of POCs (112); a dose-response relationship also appeared to be present. This may be due to suppression of immune function, increased risk of arrhythmias, impaired hemostasis and exaggerated stress response (113). The findings have been reproduced in patients undergoing lung cancer surgery showing that AUD increased risks of pneumonia by 50% (110), acute lung injury by 90% (114) and increased mortality in those consuming at least 60 g of ETOH per day by 50% (111).

The first step addressing AUD is detection. Use of a standardized questionnaire such as the Alcohol Use Disorder Identification Test (AUDIT) can increase detection rates (115), especially if it is embedded in a computer screening tool (116). Once identified, the next goal is decreasing alcohol intake. To date, however, a safe level of preoperative alcohol consumption has not been identified. While total abstinence has been advocated (113), insufficient evidence supports this approach. Realizing the full positive impact of alcohol reduction programs may be a challenge preoperatively, as up to 8 weeks may be required to reverse some of the physiologic effects of alcohol (113). Possible benefits must be weighed against risk of alcohol withdrawal. In some individuals, supervised interventions may be required (113). Overall, limited evidence in the preoperative period suggests that preoperative alcohol cessation interventions do decrease POCs (OR 0.22; 95% CI, 0.08–0.61). However this metanalysis only included 2 RCTs representing a total of 69 patients (117). Clearly, small studies such as these are at risk of both fragile results and are inadequate to address safety concerns. Planning for postoperative alcohol withdrawal syndrome (AWS) is also required preoperatively, as AWS occurs in 50% of patients of unrecognized individuals with AUD. Conversely, when AUD is detected and appropriate perioperative measures are taken, AWS occurs in only 25% of patients with AUD (111,113).

We recommend a decrease in alcohol intake as early as possible prior to surgery. For those at risk of withdrawal we recommend a decrease in ethanol intake and abstinence only if properly supervised.

Conclusions

Patients undergoing lung surgery for a cancer diagnosis are at a high risk of perioperative complications. While many characteristics that contribute to this high-risk profile are likely not modifiable, certain factors may be amenable to optimization prior to surgery. Early assessment and identification of key risk factors such as frailty, anemia, COPD, smoking, and malnutrition should allow clinicians to engage in rational strategies to improve patients' physical and physiological status before surgery. Because high-level evidence from low risk of bias randomized trials is not routinely available for these optimization strategies, clinicians are encouraged to weigh the risks and benefits of each strategy at the individual patient level. Future research efforts are urgently required to demonstrate the overall effectiveness of preoperative optimization strategies in thoracic surgery, which should support their routine inclusion in thoracic-specific ERAS protocols.

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Footnote

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